A GREAT PATHOLOGICAL FRONTIER

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IN RECENT years increasing attention has been paid to the relationship between disease and environment. Medical history contains abundant examples of successful searches for the cause of disease through studies of distribution patterns. Although this epidemiological approach has been most significantly successful in the realm of infections and vector-transmitted diseases, it is becoming increasingly recognised that the incidence of many forms of cancer and other conditions with obscure aetiology may also be related to environment.

Genetic factors also play a part in determining disease patterns and it is often difficult to distinguish the effects of hereditary tendencies from those of environmental influences.

The first step in any search for possible genetic or environmental factors that may have a causative relation to any particular disease must be an attempt to define geographical limitations of areas in which incidence is unduly high or low.

The value of such studies is likely to be related to the degree of contrast that can be shown to occur within limited distances.

A great deal of geographical pathology has been focussed around the comparison of the statistics of one country with those of another. This approach, although undoubtedly valuable, tends to overlook local concentrations of disease, especially when these overlap political boundaries, and it is crucial to remember that political boundaries are not pathological frontiers (Burkitt and Hutt 1966).

In the search for geographical variations in disease patterns, emphasis on areas of high incidence has tended to overshadow the value of confirmed negative observations. The fact that a disease is almost unknown in a particular area may be just as aetiologically significant as its high incidence in another. For a negative observation to be of real value it must be coupled with an active awareness and positive search, for it is as true of medicine as of other departments of life that we see what we look for.

Usually, rapid geographical changes in disease incidence are peculiar to one disease or a group of allied diseases and it cannot be often that the incidences of a wide variety of diseases show marked changes over the same line of geographical demarcation. Areas where such changes occur may be considered as pathological frontiers, and perhaps the greatest frontier of this nature in Africa traverses the southern half of the Sudan. Not only in pathology, but also in manner of life, building habits, genetic background, type of country, domestic animals and cultural background, there is a greater difference between northern and southern Sudan than between southern Sudan and South Africa.

The people of southern Sudan are black-skinned Negro-Nilotic tribes, Shilluks and Dinkas. In contrast the true Sudanese are Arab-speaking Muslims of Hamitic and Semitic stock.

From a purely pathological standpoint southern Sudan may be considered as a northward extension of Uganda.

Another outstanding example of an area with similar pathological characteristics and cutting across political divisions is found south-west of Uganda. Several disease patterns are common to the mountainous country that includes Rwanda, Burundi, south west Uganda, Eastern Kivu (Congo) and the extreme north west of Tanzania (Fig. 1).

The high incidence of stomach cancer and Kaposi's tumour are obvious examples, as is the virtual non-occurrence of oesophageal cancer. (Hutt and Burkitt 1965; Clemenson, Maisin and Gigase 1962). Both this area and the Sudan illustrate well how all important local disease patterns can be overlooked when studies in geographical pathology consist largely in comparisons between countries.

Before discussing some of the disease patterns that alter markedly somewhere in the region of Malakal (Fig. 1), two points must be emphasised. In the first place much credit must go to those who have shown overall cancer patterns both in East Africa and the Sudan, and in particular to the pathologists. Second, it must be stated at the outset that these are preliminary observations, formed after reference to published records for laboratories in East Africa and the Sudan and discussions with many clinicians and pathologists to whom I am indebted for all my information.
Disease Patterns that change across the Southern Sudan Frontier

A. Malignant Tumours

1. Conditions in which a high incidence is replaced by almost complete absence

(a) African Lymphoma (Burkitt, 1966)

This tumour, common throughout low country in East Africa and also prevalent in southern Sudan, is almost unknown north of the pathological frontier. Although Lynch and Hassan (1962) reported three cases there was no reference to their tribe or place of domicile. It is probable that they were southerners, as discussions with most of the surgeons in the Sudan have failed to reveal any case of this tumour occurring in a northerner. Husband saw one case in a Syrian boy. Lynch, in his report of three un-located patients with Hassan mentions seeing one patient at Juba in the south.

(b) Kaposi’s Sarcoma

This bizarre neoplasm, so rare in Europe and America but common over much of tropical Africa is particularly prevalent in north-west Uganda, and is frequently observed in southern Sudan. I only know of a single case observed in the Sudan north of the southern provinces. This was one of the most widespread examples of the tumour that I have seen, affecting a man who had spent a year in southern Sudan 17 years previously.

Husband, after nearly 20 years surgical practice at El Obeid, could not recall a single case.

(c) Ulcer Scar Epithelioma

Epithelioma developing in the scar resulting from a chronic tropical ulcer is one of the most frequently observed cancers in East Africa and the southern Sudan. It is rarely seen further north and both surgeons and pathologists in Khartoum affirmed that nearly all cases they had seen had occurred in southerners.

(d) Penile Cancer

This is the commonest male cancer in Uganda (Dodge and Kaviti 1965; Dodge, Linsell and Davies 1963), and it is one of the most frequently recognised neoplasms in southern Sudan (Nabri; Nazir, personal communications) where most of the population are pagan or Christian.

The rest of the Sudan is predominantly Moslem and the almost universal circumcision habits protect the people from this form of cancer. Husband could only recollect a single case in his long experience. Davidson P. C., estimates that three or four cases may be seen annually at Khartoum, but the majority of these may come from the south.

(e) Basal-cell Carcinoma (Rodent Ulcer)

I have only once seen this tumour in an African during 20 years in East Africa.

Most of the provincial hospitals in the Sudan, with the exception of those in the south, see one or two patients suffering from rodent ulcers each year. This tumour accounted for 3 per cent of cancer in the series reported by Lynch, El Hassan and Omar (1963) from Khartoum, and just over 3 per cent of Hickey’s (1958) series of malignant epithelial tumours.

(f) Oral Cancer

Cancer of the oral cavity, with the exception of jaw tumours, is rare in Uganda. In Davies’s series of 2926 malignant tumours seen in Uganda there were only 20 cases of cancer of the tongue, lip and floor of the mouth (0.7 per cent). In contrast, cancer of the lip and mouth accounted for over 3 per cent of cancer in the series of Lynch and others (1963). Tumour of the lips, tongue, jaws, cheeks and palate accounted for over 4 per cent of Bates’ cancer cases, and tumours of the mouth and lips made up approximately 4 per cent of Hickey’s (1958) series of epithelial tumours.
2. **Tumours whose incidence changes significantly across the pathological frontier**

(a) **Breast Cancer**

Throughout East Africa breast cancer accounts for less than 5 per cent of recorded neoplasia. Linsell (1962) recorded 4.6 per cent from Kenya, Davies, Knowelden and Wilson (1965) reported 4 per cent from Uganda, and more recent Uganda figures (Wright) were 4.25 per cent. The situation in southern Sudan appears to be similar.

In contrast breast cancer heads the list of malignant tumours in the Sudan by a wide margin, accounting for nearly 24 per cent of female cancers (an incidence nearly double that of cervical cancer) (Lynch and others 1963). Referring to breast cancer Hickey (1958) comments that “This cancer . . . . . . is the commonest single cancer seen in our laboratories. Considering the local conditions it is almost certain that it must be the commonest in the Sudan, for the women are considerably more reluctant to enter hospital than the men.”

(b) **Hepatoma**

Available evidence would suggest that this tumour is much less common in the Sudan than in East Africa. It only accounted for 1.4 per cent of cancer in the series of Lynch and others (1963) as against 6.8 per cent of a Kampala series (Davies and others 1965). It must, however, be borne in mind that the difficulty in obtaining autopsies in the Sudan may account for an under-diagnosis of this tumour. Talks with clinicians suggest that this tumour is not common.

If this difference in incidence could be substantiated it would be consistent with theories which suggest that a fungus in stored crops may have a causative relationship. The dry conditions prevailing in the Sudan in all but the south would preclude the growth of fungus.

At El Obeid, where large quantities of ground nuts are marketed, I was informed that prices obtained were good since the nuts were always well dried.

(c) **Postnasal-space Tumours**

Clifford (1965) has shown that these are unusually common in the Kenya Highlands and rare towards the coast of Lake Victoria. They are apparently much less common in Uganda. Milosev (personal communication) has shown that this tumour is relatively common in much of the Sudan, in climatic conditions almost diametrically opposite to those obtaining in the areas of high incidence in Kenya.

B. **Non-Neoplastic Conditions**

1. **Those in which a high incidence is replaced by almost complete absence**

(a) **Madura-mycosis**

This distressing condition is prevalent in several parts of the Sudan, and in particular in the Ghazira. Although Nocardia infections, clinically similar to madura-mycosis, do occur in East Africa, the black, yellow and red forms of madura infections are not seen.

(b) **Tropical Ulcers**

In contrast to madura-mycosis these are common throughout East Africa and the southern Sudan but appear to be almost unknown further north except in immigrants from the south.

(c) **Pyomyositis**

These spontaneous muscle abscesses are common throughout most of tropical Africa. They appear to be exceedingly rare north of the pathological barrier. I have discussed the problem with the majority of Sudan surgeons and only one could recall seeing a case other than in the south.

(d) **Urinary Calculi**

On average more than one patient a day with urinary calculi is admitted to the General Hospital in Khartoum. (Davidson, personal communication).

Bladder and renal stones are one of the commonest causes for admission to surgical wards throughout central and northern Sudan.

In contrast, urinary calculi are exceptionally rare throughout East Africa and southern Sudan except in immigrant populations.

2. **Conditions with marked incidence variations but which do not approach total change**

(a) **Breast Abscess**

Impressions gained from long experience in East Africa and discussions with most of the surgeons in the Sudan suggest that breast abscesses are much more commonly seen in the Sudan than in East Africa. Davidson informs me that cases are admitted almost daily in Khartoum whereas only monthly in Kampala. Mahmoud (personal communication) reported the same frequency in Khartoum north.
(b) Femoral Hernia

This condition seems to be almost unknown north of the area of pathological change. In only one of six provincial hospitals could the surgeon remember a single case. It is not uncommon in Uganda.

(c) Strangulated Hernia

This is an exceptionally rare surgical emergency in most Sudan hospitals. Four to five cases a year for 1,000 beds at Khartoum (Davidson), or one case a year for some 400 beds at Wad Medani (Mahmoud) contrast markedly with over 200 cases a year at Mulago Hospital, Kampala, and over 400 cases a year for 300 beds at Jinja, by the source of the Victoria Nile.

Discussion

The greater the changes in the incidence of any disease that can be shown to take place over a geographical area, and the more limited the area of demarcation between regions of high and low incidence, the more fruitful should be the search for responsible environmental factors.

The delineation of geographical boundaries must be the first step towards detecting factors responsible for changes in incidence. These may be either genetic or environmental, or a combination of the two, and they can be closely related. Customary practices and modes of life peculiar to certain tribes, though associated with genetic groups, constitute environment: the virtual freedom from penile cancer among those whose tribal or religious customs demand circumcision is an obvious example. On the other hand inherited constitutional defects may render certain people more susceptible to environmental influences.

It is probably true to say that most neoplastic and infective diseases are in some measure related to environment.

It is easier to understand how environmental factors operate in the case of infection. Thus the prevalence of madura-mycosis in parts of the Sudan is the product of the existence of the pathogenic organism together with its access to the human body. Tropical ulcers appear to be related to some trauma which allows the entry of a fusiform bacillus. In neither case is the source of infection really understood.

Of the other infective conditions mentioned above the cause of pyomyositis remains quite obscure, and the varying incidence of breast abscesses has not been explained.

The great disparity in the prevalence of hernias is the only condition mentioned that may be due mainly to genetic factors resulting in anatomical defects.

Urinary calculi probably result from a combination of environmental and genetic factors. Black Africans are almost free from this ailment in a climatic environment which seems to render other groups unduly susceptible. I was informed that the Nyla shepherds in western Sudan exist on minute quantities of water and yet rarely suffer from urinary calculi.

Of the tumours mentioned rodent ulcer is probably the only one largely influenced by racial characteristics. Deeply pigmented skin appears to confer an immunity in an environment of sunshine which predisposes to the development of this tumour in paler skinned people. Hereditary factors probably also determine susceptibility to the development of Kaposi's Sarcoma. In South Africa the condition is very much commoner in the Bantu than in white or coloured populations (Oettle, 1964). The variations in incidence in East Africa, however, suggest some additional factor as the emerging patterns do not appear to correspond to ethnic groups.

The African lymphoma is related to climatic factors and apparently to insect vectors. Ulcer scar epithelioma is also environmental, being dependant on the cause of the original ulcer and possibly subsequently on sunlight. (Shepherd, personal communication).

It seems likely that the high incidence of primary liver cancer in many parts of Africa is related to local conditions. Malnutrition with resultant liver cirrhosis has been suggested as a possible causative factor, as have toxins from fungi contaminating grain and other crops stored under damp conditions. These are still only hypotheses.

It is evident that a wide variety of factors, chemical, climatic, dietetic, domestic, traumatic or infective, must be considered in the search for circumstances that predispose to particular forms of cancer or non-neoplastic diseases.

Summary

It has been shown that the incidence of a number of different conditions, both neoplastic and non-neoplastic, change significantly across the southern Sudan in a longitudinal direction.

Some of these have been enumerated and possible environmental or genetic factors considered.

For all the information contained in this paper I am indebted to clinicians and pathologists in both East Africa and the Sudan. I have received so much willingly offered help, guidance and encouragement that it would be invidious to mention selected names.

I am grateful to the Medical Research Council, the Department of Overseas Development and the British Empire Cancer Campaign who have provided financial and other help to make these studies possible.

I also wish to thank Miss Christine Shenton for secretarial and other help.

The figure is acknowledged with gratitude to Mrs. Audrey Wesch.
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A great pathological frontier.

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*Postgrad Med J* 1966 42: 543-547
doi: 10.1136/pgmj.42.491.543

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